

THE EFFECT OF A HORMONE OF THE ADRENAL CORTEX (17-HYDROXY-11-DEHYDROCORTICOSTERONE : COMPOUND E) AND OF PITUITARY ADRENOCORTICOTROPHIC HORMONE ON RHEUMATOID ARTHRITIS*

PRELIMINARY REPORT

BY

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The adrenal cortical hormone 17-hydroxy-11-dehydrocorticosterone, hereinafter called "compound E" (Mason and others, 1938 ; Reichstein and Shoppee, 1943) has been administered to fourteen patients with severe or moderately severe rheumatoid arthritis. In each case improvement in clinical features and in sedimentation rates began to occur within a few days. When administration of the hormone was discontinued, the disease generally relapsed promptly.

Essentially similar clinical results accompanied by various biochemical effects were obtained from the administration of the pituitary adrenocorticotrophic hormone to two patients.

The rarity of these compounds presently and in the immediate future, and the limited scope of our preliminary data (especially regarding prolonged administration) make inappropriate now the use of the term "treatment" except in an investigative sense. This paper is presented, not as a clinico-therapeutic report, but as a study of certain physiologic effects which these new hormones exert on rheumatoid arthritis.

Antecedent Work

Since 1929 one of us (Hench, 1933, 1934, 1935, 1938a, b, c, 1940, 1949) has studied the beneficial effects of pregnancy and jaundice on rheumatoid arthritis. Results of these and other studies led us to the following conclusions. Even though the pathologic anatomy of rheumatoid arthritis is more or less irreversible, the pathologic physiology of the disease is potentially reversible, sometimes dramatically so. Within every rheumatoid patient corrective forces lie dormant, awaiting proper stimulation. Therefore, the disease is not necessarily

a relentless condition for which no satisfactory method of control should be expected. The inherent reversibility of rheumatoid arthritis is activated more effectively by the intercurrent of jaundice or pregnancy than by any other condition or agent thus far known. Regardless of the supposed "validity" of the microbic theory, rheumatoid arthritis can be profoundly influenced by phenomena which are primarily biochemical.

It became increasingly difficult to harmonize the microbic theory of the origin of rheumatoid arthritis with the phenomenon of relief of the disease by jaundice or pregnancy. It became easier, rather, to consider that rheumatoid arthritis may represent, not a microbic disease, but some basic biochemical disturbance which is transiently corrected by some incidental biologic change common to a number of apparently unrelated events. It seemed logical to suppose that what causes relief of rheumatoid arthritis in pregnancy is closely related to, if not identical with, that which relieves the same disease in jaundice ; if so, it could be neither hyperbilirubinemia nor a unisexual (female) hormone since neither of these is common to both pregnancy and jaundice. It was believed that the discovery of some biochemical denominator common to various agents or states beneficial in rheumatoid arthritis, but common especially to jaundice and pregnancy, would provide us with an improved treatment or control of the disease.

Finally, it was conjectured that the hypothetical common denominator or "antirheumatic substance X" was not a disintegration product from a damaged liver, but probably was a biologic compound specific in nature and function, a compound which was normal to the human organism (Hench, 1935, 1949). But if this was true, we had no certain clue as to its chemical nature or the organ of its origin.

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Earlier Investigative Therapy

In an attempt to reproduce the effects of jaundice or pregnancy we and others used more or less empirically, many agents and measures, some related to jaundice, some to pregnancy. These included the transfusion of blood from jaundiced (Hench, 1938b) or pregnant donors (Barsi, 1947), the administration of female hormones and various biliary products (Hench, 1938b), the production of experimental hyperbilirubinaemia (Hench, 1938c; Thompson and Wyatt, 1938) and of induced jaundice by means of toluylene diamine (Hench, 1938b), icterogenic serum (MacCallum and Bradley, 1944; Gardner and others, 1945; Rennie and Fraser, 1946), or lactophenin (Hench, 1949; Hanssen, 1942). The latter two agents produced articular remissions, but the mechanism of relief was not apparent.

In time we conjectured that the antirheumatic substance X might be an adrenal hormone. This conjecture was strengthened by the knowledge that temporary remissions of rheumatoid arthritis are frequently induced by procedures which are now known to be capable of stimulating the adrenal cortices, such as general anaesthesia or surgical operation (Hench, 1949). In 1938 we administered to several rheumatoid volunteers lecithin separated from the adrenal gland, not as an adrenal product *per se*, but in an attempt to induce hyperlipaemia such as may occur in association with pregnancy and jaundice. In January 1941 we recorded our interest in adrenal cortical fractions in general and in Kendall's compound E in particular, and we used briefly Kendall's cortical extract. But compound E was not available to us until September 1948. In requesting a supply for our investigation from Merck and Co., Inc.,* we expressed the belief that if any adrenal compound was in fact the agent by which rapid amelioration of rheumatoid arthritis by jaundice or pregnancy is accomplished, "we would expect to see some results within a very few days".

Compound E for Rheumatoid Arthritis

Initial Case.—The first patient for whom compound E was used was a married woman 29 years old who had severe rheumatoid arthritis of four and a half years' duration. She had not responded satisfactorily to many treatments. She was admitted to the Mayo Clinic and the hospital on July 26, 1948. Many joints were stiff, swollen, tender, and painful on movement. Radiographs revealed destructive changes in her right hip, because of which she limped, and less extensive changes in other

joints. The sedimentation rate (Westergren), 75 mm. on July 27, increased and was 109 mm. on Aug. 24, and 108 on Sept. 3.

She volunteered to take lactophenin orally, in the hope that jaundice would result and produce a significant remission. But jaundice did not develop, and no significant clinical or biochemical alterations occurred.

On Sept. 20 the patient's joints were worse than they had been. On Sept. 21 she could hardly get out of bed. On that day we began the daily intragluteal injection of 100 mg. of compound E. During that day no change was apparent; walking was so painful that she ventured only once from the room. On Sept. 22 her improvement did not appear significant to us. But when she awoke on Sept. 23 she rolled over in bed with ease, and noted much less muscular soreness. On Sept. 24, painful morning stiffness was entirely gone. Scarcely able to walk three days previously, the patient now walked with only a slight limp. Her appetite was increased.

By Sept. 27, a week after the administration of compound E was begun, articular as well as muscular stiffness had almost completely disappeared, and tenderness and pain on movement, and even swellings, were markedly lessened. The next day she shopped downtown for three hours, feeling tired thereafter, but not sore or stiff. Menses began on Oct. 1 and were unaccompanied by her usual menstrual flare-up in joints.

After eight days of use of a daily dose of 100 mg., the dose was reduced to 50 mg. daily for four days, then 25 mg. daily for ten days. But these doses were inadequate. Rheumatic symptoms increased. The sedimentation rate, which had decreased (slower than in later cases or than later in this case) from 111 to 86, increased to 118. The subsequent course of this patient will be discussed hereinafter.

Selection of Patients.—Since the fall of 1948 we have given compound E more or less continuously to five rheumatoid patients, and for periods of eight to sixty-one days to nine other patients; a total of fourteen patients.* None had mild or moderate disease. All had "moderately severe" or "severe" chronic polyarticular rheumatoid arthritis of four and a half months' to five years' duration, not satisfactorily responsive to much previous therapy. Three patients whose disease was of relatively short duration (4.5, 5, and 5 months) were already considerably disabled by rapidly progressive arthritis.

The condition of our first two patients was among the worst: one walked with considerable difficulty; the other had polyarthritis of many peripheral joints and rheumatoid spondylitis. The third patient had been using crutches for seven months. The fourth, ninth, and tenth patients were temporarily bedridden by acute flare-ups; the seventh patient was using a wheel chair except for a few halting steps. Two of the patients had early flexion deformities of knees. Some were ambulatory,

* Merck & Co., Inc., who have supplied compound E for this study have expressed their regret that because of the exigencies of manufacture no supplies of compound E are expected for treatment or additional research until some time in 1950 at the earliest, at which time supplies still will be exceedingly small.

* Two more patients with rheumatoid arthritis are now receiving compound E acetate (see Table).

but required help to get in or out of bed or off the toilet.

Sedimentation rates, before the use of compound E, were (in the order of cases): 108, 118, 51, 37, 65, 47, 103, 50, 81, 115, 64, 68, 71 and 62, mm. in one hour (see Table).

Method of Study.—To avoid undue reliance on subjective improvement, we, before, during and after giving compound E, used special charts for the examination of joints, and made moving pictures of all patients to show their changing condition. Many biochemical tests were made. Five of the patients were studied in the metabolic unit of the Mayo Clinic.

Controls.—To provide adequate controls, the

intragluteal injection of compound E was in some cases preceded, and in other cases replaced, by the injection of a fine aqueous suspension of cholesterol (100 mg. used daily for six to twenty-four days) indistinguishable in appearance from compound E. The times when the control solution and the adrenal hormone were interchanged were unknown to the patients and were, for five weeks, unknown even to the three clinical authors who were evaluating the results. When injection of the control solution was first commenced, no outstanding clinical or biochemical alterations occurred until the control solution was replaced by the cortical hormone. Likewise, when the hormone was replaced by the

TABLE 1
CERTAIN CLINICAL AND LABORATORY EFFECTS OF COMPOUND E AND OF ACTH
ON RHEUMATOID ARTHRITIS

Case	Sex	Age	Chronic arthritis		Administration of compound E or E acetate, duration	Initial clinical improvement results; degree of	Sedimentation rates				
			Duration	Severity			Effect of hormone : rate reduced, mm.			Increase in rate, mm., after hormone discontinued*	
							From	To	After	To	After
1	F.	29	4½ yr.	Severe	6 months	Marked	108	26	3 mo.	Use of hormone just discontinued	
2	M.	41	5 yr.	Severe	1st period: 11 wk. 2nd period: 3 mo.	Marked Marked	118 114	50 59	8 wk. 11 wk.		
3	M.	64	3 yr.	Severe	1st period: 60 days 2nd period: 14 wk.	Marked Marked	51 96	8 13	22 days 22 days		
4	M.	41	2 yr.	Moderately severe	1st period: 12 days 2nd period: 36 days	Marked Marked	37 43	16 11	15 days 6 days		
5	M.	34	4½ mo.	Very severe	3 months	Very marked	65	11	12 days		
6	F.	49	3 yr.	Severe	10 days	Marked	47	14	10 days	70	12 days
7	F.	53	2 yr.	Moderately severe	24 days	Very marked	103	14	30 days	58	11 days
8	M.	62	5 mo.	Severe	9 days	Very marked	50	10	9 days	38	8 days
9	F.	44	2 yr.	Severe	25 days	Very marked	81	17	17 days	76	5 days
10	M.	49	5 mo.	Moderately severe	61 days	Marked	115	13	35 days		
11	F.	40	5 yr.	Moderately severe	8 days	Very marked	64	14	10 days	70	20 days
12	F.	43	10 mo.	Moderately severe	42 days	Marked	68	22	11 days		
13	F.	31	4 yr.	Moderately severe	30 days	Marked	71	13	26 days		
14	F.	45	5 yr.	Moderately severe	21 days	Marked	62	31	21 days		
15	M.	29	3 yr.	Severe	†						
16	M.	49	10 mo.	Very severe	†						

Two patients (6 and 14) who also received ACTH

6	F.	49	3 yr.	Severe	12 days	Very marked	78	5	12 days	90	9 days
14	F.	45	5 yr.	Moderately severe	12 days	Very marked	93	18	9 days	85	6 days

* When rates in this column are not given, either the patient was still receiving compound E or its use had just been discontinued.
† Started April 3, 1949. Clinical results not mentioned in discussion.

control solution, articular and muscular symptoms recurred within a few days and sedimentation rates rose.

Preparations of Compound E.—Preparations used since December 1948 have been of greater chemical uniformity and perhaps of greater potency than those used earlier. The early preparations used for our first three patients were potent and devoid of side effects. Then certain difficulties were encountered. For reasons which are not clear, articular flare-ups promptly occurred and sedimentation rates rose quickly, coincident with the use of two different preparations. Other problems were overcome. In earlier preparations the crystals were fairly large, a possible cause of delayed absorption. Special techniques have provided suspensions of small crystals, 5 to 10 microns in size, easier to administer and to absorb. The crystals have been suspended in saline solution in a concentration of 25 mg. per cubic centimetre.

Between September 1948 and January 19, 1949, we used compound E. We then discovered that the less expensive and more easily prepared E acetate was absorbed with sufficient promptness. Since then we have used E acetate.

The preparation of the compound E used in this work has represented a co-operative effort of considerable magnitude by research chemists of Merck and Co., Inc., and by Kendall and his associates of this Clinic. Our special appreciation is due to Dr. Randolph Major, Vice-President, to Dr. James M. Carlisle, medical director, and their associates of Merck and Co., Inc. Despite intense effort, our supplies of compound E have been strictly limited because its preparation by present methods is very difficult, time-consuming, and expensive. Many uncertainties and inadequacies in this preliminary report have resulted from our inability in some cases to increase the dose at critical points, and in other cases to continue any medication after an allotted few days.

General Plan of Dosage.—With little to guide us except the experience of Sprague and his associates (unpublished) with two Addisonian patients who received 50 and 100 mg. respectively of compound E acetate daily, we fortunately started using 100 mg. daily. We have since found that smaller daily doses of 25 to 50 mg. are generally inadequate or ineffective. To date we have no definite evidence that multiple small doses are superior to one large daily dose of either compound E or its acetate.

In earlier cases the total dose of compound E used on the first day was the same (100 mg.) as that used on later days. One hundred milligrammes of E acetate is the chemical equivalent of about 89 mg. of compound E. Because of the slightly higher molecular weight and slower absorbability of the

acetate, we administered in later cases 300 mg. of acetate on the first day, and usually 100 mg. daily thereafter. This scheme gives better results, but probably will be improved.

After we obtained in each case the initial optimal improvement from this scheme of dosage (generally within seven to fourteen days), we reduced the daily dose in several cases to 75, 50, or even 25 mg., hoping to find a small, economical, effective "maintenance dose". Generally, articular flare-ups occurred and sedimentation rates rose promptly. So far a minimal daily dose of 75 to 100 mg. seems required, and sometimes such a dose does not entirely control symptoms and sedimentation rates. Perhaps small doses will be sufficient in cases in which the disease is mild.

Additional Measures.—Whatever analgesic agents, physical therapy, or other remedies were being administered, use of them was stopped several days to three weeks before compound E was employed. The factor of "hospitalization" (rest in bed, inadvertent "psychotherapy") was unavoidable, but except as they were disabled the patients were ambulatory and, when improved, were encouraged to assume as much activity as convenient, inside and outside the hospital, such as walking and shopping downtown. One patient, a local physician, eventually was given compound E as an out-patient after he returned to work.

Clinical Effects of Compound E

Initial Effects on Muscles and Joints.—In each of the fourteen patients the initial results were as follows. Within a few days there was marked reduction of stiffness of muscles and joints, lessening of articular aching or pain on motion and tenderness, and significant improvement of articular and muscular function (Table). A pattern of improvement was evident. Usually the fibrositic component (muscular and articular stiffness) began to diminish first, often within the first forty-eight hours after use of the hormone was begun, and often was markedly or completely relieved within a few days. Second, articular tenderness and pain on motion were lessened. Then articular swellings generally diminished, sometimes fairly rapidly and completely, occasionally tardily and incompletely (perhaps a matter of dosage). In three cases mild flexion deformities of knees or elbows disappeared within seven to ten days. In another patient (Case 6) a knee, flexed at 165°, straightened to 175° after the use of compound E for ten days, flexed again to 150° when the control injections of cholesterol were being given, and later straightened to 180° when adrenocorticotrophic hormone was employed.

Those who had found the following manoeuvres difficult or impossible often were able within a few days to do them much more easily or even "normally": getting in or out of bed unassisted, rising from chairs or toilets, shaving, washing the hair or back of the neck, opening doors with one hand, wringing a wash cloth, lifting a cup or book with one hand, and climbing stairs.

Other Clinical Effects.—

The appetite often was rapidly improved. Several patients gained weight on routine diets; for example, 21.5 lb. in ten weeks; 17.5 lb. in two months; 19 lb. in forty days; 15 lb. in twenty-seven days; 7.5 lb. in twenty-six days. Improved strength was frequently noted. Several patients stressed the loss of the "toxicity" of the disease and experienced a marked sense of well-being. This euphoria apparently represented not mere relief from pain but a positive factor accompanied by increased mental capacity and activity, sometimes to the point of mild "comfortable" insomnia. We called the attention of our psychiatric colleagues to this euphoria and they are carrying out a series of observations on it.

Effects when Short-term Administration was discontinued.—Compound E was given to nine of our fourteen patients for only eighty to sixty-one days. Then, unknown to the patients, injection of the hormone was abruptly replaced by injection of the control preparation, cholesterol. In eight of the nine cases symptoms began to return or to increase promptly, generally within two to four days. The arthritis returned slowly in most cases, and rapidly in two. Sedimentation rates usually increased promptly, occasionally to more than was noted before the hormone was given (Table).

One patient, a farmer's wife, came in a wheel chair, improved markedly after injection of the hormone, and was soon walking well. Her sedimentation rate decreased 89 mm. (from 103 to 14 mm.) in thirty days (Case 7). Then the hormone was replaced by cholesterol. Although the sedimentation rate began to rise promptly (to 58 mm. eleven days after use of the hormone was stopped), she maintained practically all of her improvement for twenty-three more days in the hospital and for at least five weeks since returning to the farm and house work.

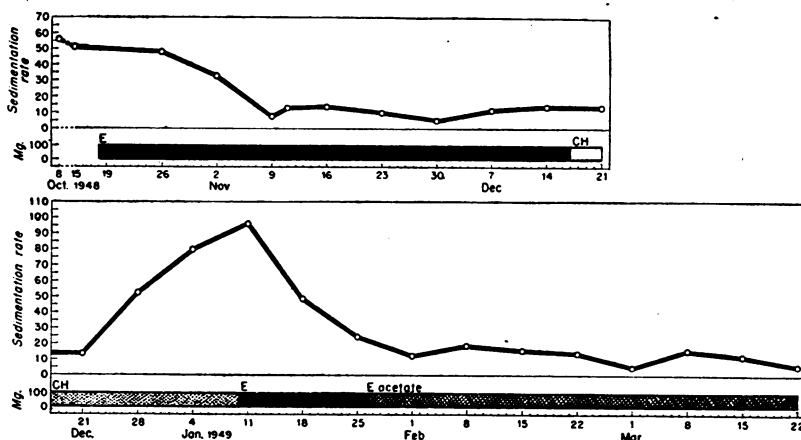


FIG. 1 (Case 3).—The effect on the sedimentation rate of compound E or E acetate, given for two separate periods to a 64-year-old man with severe rheumatoid arthritis of three years' duration. Note that the sedimentation rate rose when the control solution, CH (cholesterol), was substituted for compound E.

We hope that in other patients such relief will continue after injections are stopped more often than has occurred so far in our small series of patients with rather severe rheumatoid arthritis.

Effect of Repeated or Prolonged Administration.—Two patients (Cases 2 and 3) improved satisfactorily during eleven and eight weeks of injections, relapsed promptly but partially when the hormone was replaced by cholesterol for seventeen and twenty-four days, respectively, and again improved strikingly after use of the hormone was resumed in January. Each is now almost free from symptoms (Fig. 1).

A local physician (Case 4) was relieved by each of two periods of use of compound E and became worse in each interim. His sedimentation rates reacted appropriately. He said: "When I take the injection I lose completely my most distressing symptom, 'toxicity'; also all of my fibrositis and most but not all of my arthritis. All I have left is arthritis in miniature."

The hormone has been given daily, in varying doses, to one patient since Sept. 21, 1948, and to another since Dec. 24. In the latter case (Case 5) a daily dose of 100 mg. of compound E or E acetate has controlled symptoms completely for most, but not all, of the time. The patient occasionally has "arthritis in miniature" for a few days.

The condition of our first patient, described previously, has been the most difficult to control. Although her arthritis was effectively abated, it has never been completely relieved by continued daily doses of from 75 to 100 mg. of compound E or E acetate. Minor articular flare-ups have often occurred. Sometimes when the usual dose was employed, but especially when larger doses were utilized to control the flare-ups, interesting

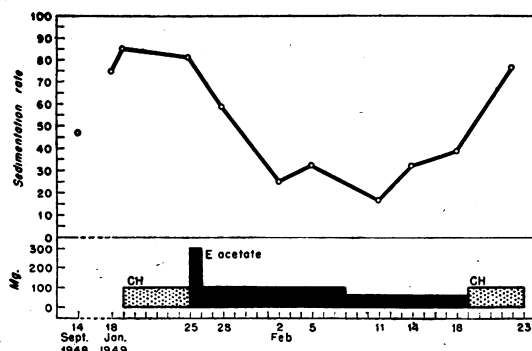


FIG. 2 (Case 9).—Effect of compound E acetate on the sedimentation rate of a 44-year-old woman with severe rheumatoid arthritis of two years' duration. Note that at first the sedimentation rate was not affected by the control solution, CH (cholesterol); then the rate decreased notably when an adequate dose of compound E acetate was used; then it increased when the dose of E acetate was reduced to 50 mg.; finally, when the use of compound E acetate was discontinued and cholesterol was substituted, the sedimentation rate increased markedly.

and important phenomena occurred. The patient would suddenly gain 4 to 7 lb. within two to four days, and then as suddenly lose the excess by way of spontaneous diuresis. There appeared some acne, mild hirsutism, and rounding of facial contour. Her menses, always irregular, ceased recently. In this one case prolonged use of the hormone presumably has induced a temporary endocrine disturbance which is being studied in the metabolic unit.

Much more experience is needed before we shall know how effective or safe the prolonged administration of compound E will be.

Laboratory Effects of Compound E

Sedimentation Rates.—In every case, when compound E or its acetate was employed, sedimentation rates decreased markedly; sometimes promptly and rapidly, sometimes more slowly (Fig. 2). In a few cases the rate was refractory the first three to nine days, despite marked clinical improvement (Fig. 1). Sedimentation rates usually decreased at the "moderate speed" of 2 to 4 mm. daily average, in other cases "rapidly" at a daily average of 4 to 7 mm., occasionally at the "very rapid" rate of more than 7 mm. daily. Rates of decrease varied from patient to patient and from time to time in the same patient, and were influenced by the dose of our different preparations of compound E. Most rates became normal within ten to thirty-five days (Table), but rates, although much reduced, did not become normal in Cases 1, 2, and 14.

Serum Proteins.—When serum globulin was increased and albumin-globulin ratios were low or

reversed, the use of compound E, if continued longer than a few days, lowered concentrations of globulin and normalized albumin-globulin ratios.

17-Ketosteroids.*—Urinary concentrations, which usually were in the low normal range were reduced by the use of compound E, and thereafter were sometimes but not always reduced still more for a little while, then increased, but remained in the low normal and even subnormal range.

Corticosteroids.*—The excretion of corticosteroids in the urine always increased when compound E was used. Usually there was a peak of a few milligrammes (not more than 5), which was followed by a decline to a fairly constant level between 1 and 2 mg.

Haemoglobin.—In four anaemic patients given the hormone for several weeks the haemoglobin increased 1.4, 1.8, 2, and 2 g. per 100 c.cm. In two others given the hormone for only ten to twenty days, values rose 0.5 and 1.4 g.

Erythrocytes.—In patients given the hormone more or less continuously, counts increased by 500,000 to 1,000,000 cells per cubic millimetre within a few weeks.

Relation of Dose of Compound E to Effects

Generally, but not always, symptoms and sedimentation rates responded coincidentally. When rates were temporarily refractory, an increased dose (150 to 200 mg. daily) utilized for several days, as a rule caused rates to decrease. It has been somewhat "easier to control the patient than his chart". Obviously, doses must be individualized.

Effects of Compound E on Synovial Disease

Articular biopsy has been carried out on four patients before, but thus far on only one of these same patients after, use of the hormone. The specimen of synovia removed from a knee forty-three days after injection of the hormone was begun was not normal, but histologically showed evidence of healing, and much less inflammation than did the specimen from the same knee beforehand.

Toxicity and Overdosage of Compound E

Satisfactory criteria for the chemical and physical properties of compound E and its acetate have been established. But before this was accomplished the use of two early samples coincided with the occurrence of articular flare-ups, stuffiness of the ears, and mild dizziness. We observed no notable reactions of toxicity when later preparations of

* We are indebted to Dr. H. L. Mason of the Clinic for determination of the 17-ketosteroids and corticosteroids.

compound E or E acetate were used. Transient pain in the epigastrium developed in one patient. Use of the agent was stopped for four days, then continued for many days without recurrence of symptoms. Transient oedema, generally pretibial, has occurred occasionally. It disappeared, sometimes spontaneously, or when the dose of the hormone was reduced, or when potassium nitrate was employed orally. The effects of the hormone on electrolyte and water balance are being studied.

As stated previously, symptoms presumably related to overdosage occurred in one case in which the hormone was used continually since Sept. 21, 1948. Experiences with other types of hyperadrenalism lead us to believe that this condition is reversible.

Use of Related Compounds in Rheumatoid Arthritis

We are investigating the effects of related compounds, such as dehydrocorticosterone (compound A) (Mason and others, 1937), 17-hydroxycorticosterone (compound F)* (Mason and others, 1938; Richstein and Shoppee, 1943), desoxycorticosterone (DCA) (Steiger and Reichstein, 1937), certain adrenal cortical extracts, and pituitary adrenocorticotrophic hormone (ACTH).

Effect of Pituitary Adrenocorticotrophic Hormone (ACTH) on Rheumatoid Arthritis

Two female patients with severe rheumatoid arthritis received 100 mg. of adrenocorticotrophic hormone intramuscularly for twelve days.† Results of metabolic studies will be reported separately. Marked clinical improvement essentially similar to that resulting from the use of compound E occurred promptly. Within a few days there was striking reduction of stiffness, pain on movement, and articular tenderness. Sedimentation rates decreased even more promptly and steadily than when compound E was employed: from 93 to 18 mm. within nine days in one case (Fig. 3); from 78 to 5 mm. within twelve days in the second case.

Side effects resulted from: (1) small amounts of posterior pituitary extracts with the adrenocorticotrophic hormone, and (2) the biochemical alterations induced by adrenocorticotrophic hormone. Noted were a sense of exhaustion, transient gas pains, heaviness in the chest and moderate elevation (20 to 40 mm.) of blood pressure.

There were alterations in blood and urine chlorides, in electrolytes and the carbon dioxide

combining power of the blood, and in the excretion of 17-ketosteroids and corticosteroids in urine.

Both patients also received compound E either some time before or after the use of adrenocorticotrophic hormone. Relief from symptoms of arthritis was about the same when either hormone was employed; when the use of either was discontinued the symptoms of arthritis and sedimentation rates quickly increased.

Effect of Dehydrocorticosterone (Compound A)

A woman with severe rheumatoid arthritis who later responded very well to compound E and to adrenocorticotrophic hormone was not benefited by the intramuscular use of 100 mg. of compound A daily for seven days. Two more patients are now receiving compound A.

Rheumatoid Arthritis and Its Relationship to Certain (Other) Non-microbial Arthritides

The syndrome of Addison's "disease" results whether the adrenal glands are impaired by atrophy, tuberculosis, or tumour. To what extent could rheumatoid arthritis be merely a syndrome produced by any factor which causes a deficiency of adrenal hormone? Do some of the non-microbial arthritides usually considered "specific" (such as the arthritis of lupus erythematosus, of psoriasis, of chronic ulcerative colitis, or even of acute gout and rheumatic fever) represent likewise a transient deficiency of adrenal hormone, merely an "adrenal complication" of different parent-diseases, are some of these articular complications essentially identical with "rheumatoid arthritis"?

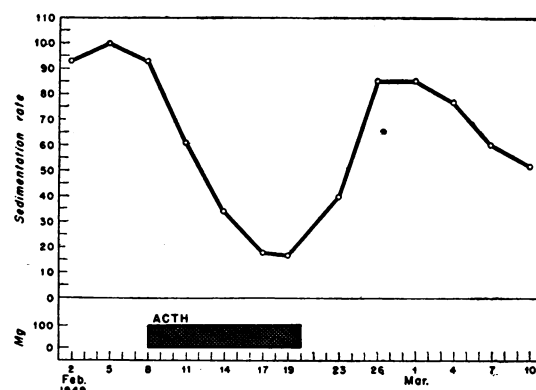


FIG. 3 (Case 14).—Effect of pituitary adrenocorticotrophic hormone (ACTH) on the sedimentation rate of a 45-year-old woman with moderately severe rheumatoid arthritis of five years' duration. The rate decreased markedly during the use of ACTH, then increased rapidly. Note the "rebound" between February 26 and March 10; thereafter the rate increased again.

* We are indebted to Dr. E. Gifford Upjohn of the Upjohn Company for the sample of 17-hydroxycorticosterone (compound F).

† We are indebted to Armour and Company, and particularly to Dr. John R. Mote, director of medical research for that company, for supplies of this pituitary hormone.

Application of the Use of Adrenal and Pituitary Hormone to Conditions other than Rheumatoid Arthritis

With the aforementioned conjectures in mind, we are giving compound E to a patient with severe lupus erythematosus and polyarthritis and to another with acute rheumatic fever. The encouraging results will be reported later.

Listed elsewhere (Hench, 1949) were several conditions usually relieved by jaundice or pregnancy or both. The mechanism of relief may become less mysterious if some of these conditions are found to be responsive to compound E, and others to adrenocorticotrophic hormone, which of course stimulates the production of not one but several adrenal hormones. A patient who had myasthenia gravis, treated at the Mayo Clinic by Eaton and Sprague (unpublished data), was unrelieved by the daily use of 100 mg. of compound E for twelve days, but a patient with this disease treated elsewhere was relieved by adrenocorticotrophic hormone (Soffer and others, 1948). The inference is obvious.

It is of course most unfortunate that the available amounts of compound E and of adrenocorticotrophic hormone are so small and may remain so for months to come. The production of compound E by partial synthesis is being expanded; total synthesis may be an eventuality. The supply of adrenocorticotrophic hormone, a complex protein, depends on the availability of pituitary glands. Opportunities to enlarge the scope of these investigations in the near future appear to depend on improvements in the production of compound E.

Conclusions

Certain clinical and biochemical features of rheumatoid arthritis have been markedly improved by the daily intramuscular injection of either the adrenal cortical hormone, 17-hydroxy-11-dehydrocorticosterone (compound E), or the pituitary adrenocorticotrophic hormone, ACTH. Articular, muscular, and other symptoms were lessened notably, and sedimentation rates were reduced when either hormone was employed; when the use of them was discontinued symptoms and signs of rheumatoid arthritis usually, but not always, returned or increased promptly.

Certain clinical facts and theoretic considerations combine to suggest that these adrenal and pituitary hormones may be useful against other rheumatic diseases and against certain non-rheumatic conditions which are generally relieved by pregnancy or jaundice.

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Effet de l'Hormone Corticale de la Surrénale (17-Hydroxy-11-Dehydrocorticostérone : Composé E) et de l'Hormone Pituitaire Adrénocorticotrophique sur l'Arthrite Rhumatismale

CONCLUSIONS

Des injections intramusculaires de l'hormone corticale de la surrénale, 17-hydroxy-11-dehydrocorticostérone (composé E) ou de l'hormone pituitaire adrénocorticotrophique, ACTH, ont amené une amélioration notable de certains caractères cliniques et biochimiques de l'arthrite rhumatismale. Les symptômes articulaires, musculaires, et autres ont accusé une regression marquée et le taux de la sédimentation globulaire a baissé, les deux hormones agissant séparément d'une façon similaire. Généralement, mais pas toujours, l'interruption du traitement était rapidement suivie du retour ou de l'accentuation des signes et des symptômes de l'arthrite rhumatismale.

L'ensemble de certains faits cliniques et des considérations théoriques semble montrer que ces hormones, la corticale et la pituitaire, peuvent être utiles contre d'autres affections rhumatismales et contre certaines affections non rhumatismales, susceptibles d'être soulagées par une grossesse ou par un ictère.